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CLINICAL TRIALS OF ORAL CONTRACEPTIVES*

BY

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It has been known for some years that the steroids existing in nature could inhibit ovulation in woman. Practically, however, these steroids were not of value as anti-fertility agents, because of either the undesirable side-effects produced or the lack of therapeutic effectiveness on continued therapy. For example, testosterone produces undesirable androgenic effects; progesterone requires very large doses and its action is too variable; and oestrogens, although they will inhibit ovulation in some cycles, are claimed by some workers not to do so in every cycle (Drill, 1959); while long-term administration of oestrogen is complicated by irregular menstrual bleeding, which may be heavy.

Pincus and his colleagues in 1955 first found that some newer orally active steroids, mostly 19-nor compounds, would inhibit ovulation in the rat and the rabbit. This finding initiated extensive endocrinological and clinical testing of these compounds. Over 200 new steroids have been tested, but the two which have been most used are norethisterone and norethynodrel. Norethynodrel, which has been subjected to most intensive study by Pincus and his colleagues, appeared to be particularly interesting, as it was the first steroid to possess both progestational and oestrogenic activity in the same molecule.

These early trials showed that 10 mg. of norethynodrel ("enavid") plus 0.15 mg. of ethinyloestradiol-3-methyl ether (EO-3-ME) taken for 20 days from day 5 of the cycle was an effective contraceptive, and there was no indication of escape from contraceptive effect with time. Side-effects which occurred in a significant proportion of subjects—particularly vomiting, nausea, dizziness, headache—were found to be more frequent in the first cycle of medication and to decrease thereafter. The addition of oestrogen to the progestogen itself was found to be necessary to maintain the endometrium and prevent spotting and breakthrough bleeding, though this still occurred despite regular taking of tablets. On the whole, patients had regular bleeding and a decreased menstrual flow. Of Pincus's volunteers, 20% gave up in the first year, largely because of these side-effects, while among Tyler's more sophisticated women in Los Angeles 474 out of 715 (66%) discontinued.

As the side-effects and high cost were a disadvantage, 5-mg. tablets containing 0.075 mg. of EO-3-ME were tried and found to be equally effective, and later 2.5 mg. had been used with varying amounts of oestrogen and with apparently similar results.

These early trials were watched in this and other countries with interest and caution: would there be any harmful effects from pituitary inhibition, any possible carcinogenic effect from the administration of steroids; would fertility be restored when the tablets were discontinued? By 1959 it seemed that these anxieties were unjustified, and preliminary carefully controlled clinical trials were instituted under the auspices of the Council for the Investigation of Fertility Control (chiefly undertaken by Dr G. I. M. Swyer and Dr. Margaret Jackson) of some of the available oral progesterones. In 1960 the Medical Advisory Council gave careful consideration to the question of the advisability of using the progestational steroid norethynodrel plus oestrogen as a contraceptive under the conditions planned for clinical trials and was satisfied that it would be safe to use in the way planned. At that time the total experience of norethynodrel included over 20,000 cycles of administration in over 1,000 women, including 150 who had received norethynodrel from 12 to 21 consecutive cycles and 66 women who had taken it from 24 to 38 consecutive cycles.

Large-scale clinical trials were then initiated, the first in Birmingham, followed soon after by another in Slough, and a third has recently begun at the Family Planning Association Headquarters in London.

Thus it will be seen that the trials initiated by the Council are of two distinct kinds: first, small, carefully controlled preliminary trials of a more scientific nature, and later large-scale clinical trials.

Preliminary Trials

Before any of these substances are used in clinical trials on women, careful consideration is, of course, given to the data available from the manufacturers, including particularly the animal screening tests for acute and chronic toxicity, and for androgenic, progestogenic, and oestrogenic properties. When it is felt that enough is known at this level, the substances are used in a number of tests which have been devised for preliminary screening in women.

These tests are usually undertaken with the pure progestogen and with the progestogen with added oestrogen.

1. *An assessment of the ability to postpone menstruation in women with regular cycles.*—An appropriate dose such as 5 mg. is administered daily from the twentieth day of the cycle for 20 days. If menstruation occurs before the 20 tablets have been taken, the result is negative and the test is repeated in the following cycle with double the dose. If menstruation does not occur until after completing the course, the result is positive and the test is repeated with

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half the dose. This test gives a measure of progestational activity by which comparison with other products of known potency can be made, though it does not necessarily parallel inhibition of ovulation, etc. It also gives some indication of tolerance and acceptability and necessary dosage

2. *To assess the ability to inhibit ovulation.*—It is believed that basal temperature charts and endometrial biopsies may be confirmatory but not convincing. Measurement of pregnanediol excretion is necessary in humans. The products to be tested are given daily from the fifth day of the cycle for 20 days. Urine is collected on the eighth and ninth days and on the twentieth and twenty-first days, in 48-hour pools, and the pregnanediol excretion determined. Where inhibition of ovulation occurs there is no difference in pregnanediol excretion between the two samples.

3. *To investigate the ability to produce secretory changes in the endometrium.*—In this test, women with long-standing secondary amenorrhoea are used and are treated as follows: ethinyloestradiol 0.05 mg. daily is given for 20 days and the progestogen in whatever dose has seemed most satisfactory from previous tests is given daily from the eleventh to the twentieth day. After an eight-day gap without medication, this routine is repeated regardless of the appearance of bleeding. Endometrial biopsy is taken the day after the last pill in this second cycle of administration.

It will be seen that these preliminary tests give us some indication of the tolerance in humans and of the capacity to inhibit ovulation, and also a measure of progestational activity on the endometrium. Such data have already been collected on norethynodrel, norethisterone, norethisterone acetate, B.D.H. 1298 (6α-methyl,$\triangle$-6-17α-acetoxyprogesterone) with and without added oestrogen and in various doses, and tests are proceeding with other substances.

It is apparent so far that these compounds are all much more effective when used with added oestrogen, which rather suggests that the pituitary inhibition is also responsible for cutting down the production of endogenous oestrogen, thus necessitating exogenous administration of the latter. Although these products have similar effects on inhibition of ovulation, cervical mucus, and the endometrium, there are some interesting differences.

When a progestogen is found as a result of such preliminary tests to be suitable for use as an oral contraceptive, it is then used in a small number of women as a contraceptive. If the results are satisfactory over a few months, the product is ready for use in large-scale trials.

Large-scale Clinical Trials

Once the background data have been obtained, it is obvious that larger-scale clinical trials are necessary, the object of such trials being to establish (1) the strength of pill that will produce minimal side-effects with adequate control of conception; (2) the simplest method of administration; and (3) the acceptability of the method to women in this country.

The organization of large-scale trials is described in the preceding report (p. 1172) of the Birmingham trial (Eckstein *et al.*, 1961) and need not be repeated here.

Method of Administration.—The routine we are using differs from that of other workers, as it was decided that there was no point in repeating the same experiments. The pills are given in bottles of 20—that is, each bottle contains one month's supply. The patients are instructed to take one pill daily from the fifth day of the cycle for 20 days (the first day of the cycle is the first day of menstruation); they then stop taking pills, wait until withdrawal bleeding occurs—usually one to four days later—and start the new bottle on the fifth day of the next menstrual cycle. They are told that if no menstrual bleeding occurs they should leave five clear days and again start a new bottle of pills.

In trials elsewhere (Pincus, 1959, 1960; Pincus *et al.*, 1958, 1959; Rock, Garcia, and Pincus, 1959), the question of breakthrough bleeding has been dealt with by getting the patient to increase the dose, taking one extra tablet each day when breakthrough bleeding threatened, and to continue this until spotting disappears. It seemed to us possible that the menstrual cycle might settle down after three or four cycles and the breakthrough bleeding stop spontaneously. The regime we decided to use, therefore, was that if slight staining or spotting occurred the patient should ignore it and continue to take the tablets; if bleeding occurred which was as much in amount as normal menstruation, she should discontinue the tablets, allow the bleeding to take place, and resume them again on the fifth day of the cycle as before. It seemed to us simpler to give the patients a regular number of pills to take each month. As norethynodrel has been used most extensively it was the one chosen in the first large-scale clinical trials in this country.

Dosage Used.—As workers in other countries were already using 2.5 mg., and since it seemed to be as effective as larger doses, could be expected to give fewer side-effects, though rather more breakthrough bleeding, and had already been used with varying amounts of oestrogen, it was decided to concentrate on this dose, and to try out 2.5-mg. tablets of norethynodrel with varying amounts of oestrogen. The earliest clinical trials were undertaken by Dr. Swyer, Dr. Margaret Jackson, Dr. Helena Wright, and myself, using 2.5 mg. of norethynodrel plus 0.15 mg. of EO-3-ME. In the first trial in an F.P.A. Clinic (Birmingham 1 OC) the dose used was 2.5 mg. of norethynodrel plus 0.035 mg. of EO-3-ME, and in Slough F.P.A. Clinic a few weeks later a third strength, 2.5 mg. plus 0.1 mg. of EO-3-ME.

Birmingham 1 OC Trial

As a detailed account of this trial is given earlier in this issue (see p. 1172), all that need be said here is that it soon became obvious from the record charts of patients in the Birmingham trial that this tablet was having a different effect from the others.

The first noticeable difference with patients in the Birmingham trial was that their menstrual cycles were irregular: 20 cycles lasted 30 days or more, up to as many as 71 days; 7 were less than 25 days, with very few around the normal limits. It quickly became obvious that in fact some of the patients were pregnant, and that this tablet was not an effective contraceptive, as it seemed to *delay* ovulation rather than to inhibit it.

It would appear that when patients came to the end of 20 days' issue of tablets they had a breakthrough ovulation and consequent amenorrhoea with, in several cases, breakthrough bleeding in the middle of the next cycle. Since the 2.5 mg. with 0.1 and 0.15 mg. of oestrogen was proving efficient, it was shown that at the 2.5-mg. dose the amount of oestrogen is critical. This raises the whole question of whether 2.5 mg. of norethynodrel is a sufficiently high dose to inhibit ovulation and whether in fact tablets with a larger proportion of oestrogen have worked because of the oestrogen and not the norethynodrel. Investigations carried out in Puerto Rico by Tyler (1961) and Napp (1960) indicate that this is a sufficient dose there to inhibit ovulation. (This raises

some interesting questions of the dose required for women in different parts of the world.)

This result means, too, that we cannot use a quarter of an enavid 10-mg. tablet or half of a "conovid" 5-mg. tablet, as in the smaller dose a larger proportion of oestrogen is required.

When this failure became evident, patients in the Birmingham trial were switched over at the end of their current cycle to 5-mg. tablets of conovid—that is, tablets containing 5 mg. norethynodrel plus 0.075 mg. of EO-3-ME. In the first place the volunteers who were switched over from this tablet to the 5-mg. tablet have been analysed separately (Trial 2 OC). Later volunteers who were put straight on to the 5-mg. tablet comprise those in Trial 3 OC.

As can be seen from Table I, there is no significant difference between those who started on the 5-mg. pill and those who started on the smaller dose and were transferred to the 5-mg. pill, except that the amount of nausea in the first cycle is less among patients transferred to the higher dose. This is to be expected, as these patients had already developed some tolerance to the drug.

TABLE I

No. of Women	No. of Woman-months	Nausea	Nausea and Vomiting	Dysmenorrhoea	Headache and Faintness	Weight Increase > 3 lb. (1·36 kg.)	Weight Decrease < 3 lb. (1·36 kg.)	Breakthrough Bleeding
F.P.A. Birmingham Trial (3 OC) 5 mg. Norethynodrel + 0·075 mg. EO-3-ME								
(*a*) 35	35	43%	9%	11%	17%	17%	11%	31%
(*b*) 22	22	14%	14%	23%	9%	23%	9%	36%
(*c*) 19	19	Nil	Nil	11%	5%	16%	5%	37%
(*d*) —	31	6%	Nil	16%	6%	13%	32%	32%
Birmingham 2 OC Patients Transferred from Lower Dose to 5 mg. Norethynodrel + 0·075 mg. EO-3-ME								
(*a*) 34	34	29%	9%	9%	15%	35%	3%	18%
(*b*) 31	31	13%	6%	19%	9%	13%	6%	35%
(*c*) 30	30	7%	3%	7%	3%	7%	3%	23%
(*d*) —	70	10%	3%	3%	7%	17%	4%	24%
(*e*) —	11	9%	9%	9%	18%	18%	Nil	15%

(*a*) = 1st month. (*b*) = 2nd month. (*c*) = 3rd month. (*d*) = months 4, 5, 6. (*e*) = other months.

TABLE II.—*Analysis of Results on Different Doses of Norethynodrel and EO-3-ME*

Months	No. of Women	No. of Woman-months	Nausea	Breast Discomfort	Show	Breakthrough Bleeding
5 mg. Norethynodrel + 0.075 mg. EO-3-ME						
1	91	91	48%	30%	30%	27%
2	66	66	20%	24%	28%	25%
3	61	61	Nil	16%	20%	26%
4, 5, 6	—	184	4%	27%	15%	24%
Others	—	15	Nil	10%	12%	15%
Total	91	350				
2·5 mg. Norethynodrel + 0·1 mg. EO-3-ME						
1	35	35	54%	26%	20%	34%
2	30	30	13%	7%	3%	33%
3	26	26	4%	8%	4%	38%
4, 5, 6	—	63	Nil	9%	8%	30%
Others	—	27	7%	4%	11%	63%
Total	35	181				
2·5 mg. Norethynodrel + 0·15 mg. EO-3-ME						
1	89	89	42%	Not	9%	27%
2	75	75	24%	available	7%	34%
3	73	73	10%	for all	4%	22%
4, 5, 6	—	166	4%	patients	4%	23%
Others	—	186	Nil		2%	22%
Total	89	589				

It is possible, therefore, to add these together for a comparative analysis of the different doses. Table II is such an analysis, excluding, of course, the Birmingham 1 OC trial with the ineffective dose.

Side-effects

There seems little to choose between the different doses of tablets. The incidence of *nausea* in every case is highest in the first month at about 40% and rapidly diminishes thereafter.

There appears to be no significant *change in weight*—some patients gain, a few lose weight, but no relationship has been found between change in weight and premenstrual tension, breakthrough bleeding, or show.

Libido.—The effect on libido reported in other trials has been variable. Rock and Garcia found that in 50% of patients the libido was unchanged, in 25% it increased, and in 25% it decreased. In our trials patients are asked to record the number of times of sexual intercourse and are asked at interview whether libido has been affected. More patients claim to have increased libido ; a few to have a decrease. This seems to me, however, to be a factor which is not easy to analyse in such a statistical way—for example, we have no record of the number of times of intercourse before the trial began, and experience of my own patients leads me to doubt the significance of such figures. Thus one patient, who had not marked any intercourse on her chart for two months, said on questioning that when she had a diaphragm and put it in she felt that it was a pity not to use it and she roused her husband. Since she had been protected all the time by the pill and since she preferred her husband to take the initiative, she had waited for him to do so with this result. Another patient claimed that her libido had decreased since using the tablet, but on looking up her previous records I found that a year beforehand, when she had come for refitting of her diaphragm, she had made the same complaint. On being reminded of this she indicated that there had been no decrease since that time. At the other end of the scale is the couple who marked up intercourse 91 times in one month—whether this can really be ascribed to the pill is doubtful. It must surely have had something to do with the husband's libido.

Efficiency

In the Birmingham 1 OC trial—that is, with 2.5 mg. plus 0.035 mg. EO-3-ME—there were 14 pregnancies out of 48 women. In seven women conception probably occurred in the first cycle and in three in the second cycle. This has given some most valuable information. We know now that at this dosage the amount of oestrogen is critical and the lowest dose which will inhibit ovulation is now reasonably well known to us.

There have been no pregnancies in the Birmingham 2 OC trial—that is, in those who switched from this tablet to the 5-mg. tablet—or in the Birmingham 3 OC trial—that is, in patients joining the trial on the 5-mg. dosage. In the Slough trial with 35 patients continuing for 181 woman-months on 2.5 mg. of norethynodrel plus 0.1 mg. of FO-3-ME, there has been one pregnancy, in a patient who had taken her tablets only intermittently. There is no question of tablet failure with this patient who took only 7 out of 20 tablets in the month she became pregnant.

So far, 89 women have taken tablets containing 2.5 mg. of norethynodrel plus 0.15 mg. of EO-3-ME for 589

woman-months. There has been one pregnancy, a tablet failure, among these women. This is a patient aged 36 with two children aged 13 and 6, who had a perineal tear repaired four times, with a great deal of anxiety over pregnancy, and who claims to have had no sexual relationships for several months before starting the pill. She was extremely relaxed and confident when she first started using the pill, had amenorrhoea in the first cycle, left five clear days and started the second bottle of pills as directed. She felt extremely well in the first month but began to have nausea which did not wear off. Her weight increased and she began to be anxious shortly after starting the second course of tablets. On February 12 she was found to have a positive Hogben test and pelvic examination on February 14 confirmed the diagnosis.

The tablets were obviously taken conscientiously; the patient insists that there was no question of pregnancy before she started taking them, and I am certainly inclined to believe her. Could this be a case where the tablet failed to inhibit ovulation in the first cycle or only delayed it, or is the dose too little for this patient, or could it be that the excitement associated with renewal of intercourse after such a gap could overcome the effect of the pituitary inhibition produced by the norethynodrel? After all, this happens sometimes when a woman ovulates a second time in the cycle under such circumstances.

It is interesting to notice that Pincus found among women who conceived in his trial that most conceptions occurred in the first month, and he says, "The data suggest a greater carelessness in the early cycles of experience." On the other hand, Tyler (1959) recommended the use of a diaphragm and jelly in the first month in some cases. Is it possible that some patients are not fully covered in the first month of medication? It will be some time before we know the answer to this.

Acceptability

Much prominence has been given everywhere to the side-effects complained of by patients in the early months of using oral contraceptives, but something should be said about the positive effects mentioned by patients.

Many patients have expressed themselves as being absolutely delighted with the freedom from contraceptive measures related to coital acts, of being more confident and relaxed at intercourse, and other interesting observations have been made—for example, discharge gone, skin improved, hair less greasy, abdominal post-operative pain gone, feeling better than ever before, first orgasm ever, cut down smoking, dysmenorrhoea gone. The real indication of acceptability to the patient, however, is presumably whether she perseveres with this method, and so far the results are encouraging.

Table III is an analysis of patients who have withdrawn from the trial. It will be seen that only 25 patients are included in the group taking the 2.5 mg. plus 0.15 mg. tablets: this is because full particulars are available only for patients in one of the trials at this dosage. Considering the proportion of patients who do have some side-effects in the beginning, this number of withdrawals due to side-effects from the tablets seems remarkably small. It will be seen that nine patients out of a total of 150 withdrew for this reason.

TABLE III.—*Withdrawals*

Tablet Strength	No. of Patients	No. of Woman-months	Total No. Withdrawing	No. Withdrawing Because of Side-effects of Pill
5 mg.+0·075 mg.	91	350	7	2
2·5 ,, +0·1 ,,	35	181	5	3
2·5 ,, +0·15 ,,	25	272	6	4

5 mg.+0.075 mg. (conovid)

1. 1st month—no reason given.
2. 1st month—dizziness and blurred vision.
3. 5th month—wishing to become pregnant.
4. 3rd month—heavy feeling, amenorrhoea.
5. 6th month—aches and pains all down left side of body.
6. Husband gone away } Both may rejoin.
7. Marital difficulties }

No. due to tablet side-effects: 2 (months 1 and 3)

2.5 mg.+0.1 mg.

1. 3rd month—nausea.
2. 6th month—increase in weight.
3. 6th month—short cycles.
4. 1st month—discharge.
5. 3rd month—pregnant, due to intermittent tablet-taking only.

No. due to side-effects: 3 (months 3, 6, 6).

2.5 mg.+0.15 mg

1. Pregnant 1st month.
2. 6th month—abdominal cramp, constant lethargy, and feeling cold.
3. 14 cycles, all with breakthrough bleeding, sick headaches, abdominal cramp, and growing antipathy to taking pills for rest of life.
4. Gave up at 6th cycle because of mastitis, breakthrough bleeding in five out of six cycles, increased weight, bloated feeling.
5. Gave up after eight months because of migrainous headaches every month and depression in the period without tablets and sleeplessness, though very reluctant to stop as she liked this method of contraception very much.
6. 4 cycles: an erratic user, forgot one month, took 24 another month, frigid, dislikes birth-control methods, etc.; when I queried her over being erratic she took fright and left.

No. due to side-effects: 4 (months 6, 6, 8, 14).

Breakthrough Bleeding

To test the value of our regime, the breakthrough bleeding has to be analysed. For the purpose of our trials, breakthrough bleeding is defined as bleeding of an amount equal to that of a normal period, so that the patient stops medication.

It would appear from the figures so far that there is very little to choose between the different strengths of tablets in the first six months, as can be seen from the comparative figures for each month in Table IV. The small number of patients on the 5 mg. and the 2.5 mg. plus 0.1 mg. tablet who have continued beyond six months makes the figures for breakthrough bleeding beyond that time of little value so far. The patients, however, who have continued the 2.5 mg. plus 0.15 mg. tablet have continued for some time. Among my own 25 patients on this dose one patient has continued for 20 cycles and several for more than 12 cycles, and here the percentage of persistent breakthrough bleeding is 22%, so that, on this tablet, one can say that on this regime about 20% of patients can expect to continue to have breakthrough bleeding beyond the sixth month. There is no reason to suppose that this breakthrough bleeding is harmful in any way; endometrial biopsies repeated on patients who have continued to have such short cycles show hypoplasia of the endometrium and, in fact, suggest that a higher proportion of oestrogen in the tablet might be more effective in preventing this phenomenon.

The average *length of breakthrough bleeding cycles* on the different tablet strengths was analysed to find out if there was any difference. It has been suggested, for example, by Napp (1960), that the breakthrough bleeding tends to occur in the earlier part of the cycle on the smaller dose. This has not been our experience.

For this analysis, cycles where tablets were missed were discounted and all cycles are included where the tablets were taken conscientiously.

TABLE IV.—*Analysis of Breakthrough Bleeding Cycles*

Tablet Strength	No. of Cycles of B.T.B.	No. of Days	Average Length of B.T.B. Cycle
2·5 mg. + 0·1 mg. ..	33	700	21
2·5 ,, + 0·15 ,, ..	27	591	22
5 ,, + 0·075 ,, ..	23	465	20

TABLE V.—*Patients Transferred to 5 mg. from Lower Strength Because of Persistent Breakthrough Bleeding*

No. of Cycles of B.T.B.	No. of Days	Average Length
34	677	20

In some of the patients, where breakthrough bleeding has been persistent, an attempt has been made to control this by increasing the dosage to 5 mg. but administered in the same way. In no cases so far has this reduced the breakthrough bleeding (Table V).

On the other hand, there seems no reason to worry about breakthrough bleeding of this order where the cycles are 20 to 22 days in length, and some patients have been perfectly happy to carry on in that way.

Nevertheless, some attempts have been made to control this. Among my own patients, two who have been transferred to Schering 639 (4 mg. of norethisterone acetate + 0.05 mg. of ethinyloestradiol) have immediately settled down to a normal cycle, and two patients who have been given an increased dose in the second half of the cycle have also settled down.

The amount of menstrual flow is interesting, and I have made an analysis of my own patients (25 on 5 mg. and 25 on 2.5 mg. + 0.15 mg.) who mention any increase or decrease in the amount of flow: 22% found a decreased flow and 8% found an increased flow. In all these cases, however, those who had had heavy bleedings before treatment had less heavy bleeding during treatment, and those who claim to have earlier and prolonged bleedings had all very slight ones in the first place.

Amenorrhoea

Sometimes withdrawal bleeding fails to occur with a consequent cycle of amenorrhoea. The number of cycles of amenorrhoea in these trials has been analysed (Table VI).

TABLE VI.—*Amenorrhoea*

Tablet Strength	Cycles of Amenorrhoea	Woman-months	Percentage
2·5 mg. + 0·1 mg. ..	17	181	9
2·5 ,, + 0·15 ,, ..	3	272	1
5 mg. + 0·075 mg. ..	21	344	6

Pincus (1959) suggests that after withdrawal of medication the endogenous ovarian secretion takes over and is adequate to sustain the endometrium. The incidence of amenorrhoea reported by Pincus (1959) in trials in Humacao, Puerto Rico, and Haiti has been between 0.7% and 3.2%, so that our regime would appear to increase its incidence.

Conclusions

Much has been learnt about the mechanics of running trials of oral contraceptives.

We have discovered that with a 2.5-mg. dose of norethynodrel the amount of oestrogen is critical; 0.035 mg. of ethinyloestradiol 3-methyl ether is not sufficient combination, with the progestogen, to prevent ovulation. There is therefore not enough oestrogen in half a conovid tablet for effective use.

Bearing in mind that these patients have all proved their fertility, this would appear to be a most efficient method of contraception in the right dosage. So far 215 women have taken part in the trials for 1,120 woman-months and only one pregnancy has occurred where the tablets have been taken conscientiously.

There seems to be little to choose so far between the different doses of norethynodrel used. About 40% of the patients have some degree of nausea in the first month, but this very quickly disappears if they are encouraged to persevere. The only other important side-effect after the first month is breakthrough bleeding. The regime we have initiated in trials in this country does not appear to solve this problem. About 20% of patients can expect to continue to have breakthrough bleeding beyond the fourth cycle. While this is not considered to be harmful, it can be annoying to the patient, and it would seem advisable to have more than one product available, as such patients may settle well on another product.

It would appear that the American method of increasing the dosage when breakthrough bleeding threatens might be a better method of controlling this, but we feel that it is a clumsy method and one which could be improved upon.

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A new school curriculum introduced by the Minister of Education in Greece has abolished Latin, cut down the time spent on studying ancient Greek, instituted systematic teaching of modern Greek, and increased the time spent on teaching mathematics and physics.